



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

CH

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,515	05/01/2002	Dan L. Eaton	10466/300	8122
30313	7590	01/10/2006	EXAMINER	
KNOBBE, MARTENS, OLSON & BEAR, LLP 2040 MAIN STREET IRVINE, CA 92614			ROMEO, DAVID S	
		ART UNIT	PAPER NUMBER	
		1647		

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/063,515	EATON ET AL.
Examiner	Art Unit	
David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 20 October 2005.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-5 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-5 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

 1. Certified copies of the priority documents have been received.

 2. Certified copies of the priority documents have been received in Application No. _____.

 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date 0805, 1005.

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) 5 has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/10/2005 has been entered. Claims 1-5 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC §§ 101, 112

10 Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicants' discussion of the utility legal standard is acknowledged. However, the present rejection is based upon Applicants' failure to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the 15 technological field of the invention. Adopting Applicants' standard for utility would result in a per se rule that any disclosed difference in mRNA expression is significant, relevant, and tumor-dependent and that any such difference would require a per se rule of utility for the polynucleotide, the encoded polypeptide and antibodies thereto. The examiner declines to attenuate the utility requirement to this degree because this standard is not what the art teaches. 20 The countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-independent. See Hu (J Proteome Res. 2003 Jul-Aug;2(4):405-12), which teaches:

“[h]igh-throughput technologies, such as proteomic screening and DNA micro-arrays, produce vast amounts of data requiring comprehensive analytical methods to decipher the biologically relevant results” (Abstract).

5 “In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study” (page 405, left column, full paragraph 1).

10 “It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful. ... For genes displaying a 5-fold change or less ... there was no evidence of a correlation between altered gene expression and a known role in the disease. This reflects ... genes whose modest changes in expression may be unrelated to the disease.” Paragraph bridging
15 pages 411-412.

The examiner understands Hu’s use of the term “biologically relevant,” “biologically meaningful,” or “relevant to the study” to include diagnostic relevance, which is supported by LaBaer (Nat Biotechnol. 2003 Sep;21(9):976-7), which teaches:

20 In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. Page 976, paragraph bridging middle and right columns.

25 30 A tumor-independent detection of a change in mRNA expression cannot be used as a tumor marker. Furthermore, Gygi (Mol Cell Biol. 1999 Mar;19(3):1720-30) discloses that in any large scale analysis the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA level (page 1727, right column, full paragraph 1), which indicates that the measurement of low abundance mRNAs is more prone to error. The present specification

only presents data showing a relative difference in PRO874 mRNA levels. There is no evidence that PRO874 mRNA was highly expressed.

The countervailing evidence also shows that the skilled artisan would not know if or how expression of the PRO874 polypeptide would change in tumors because there are numerous 5 levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. See:

Haynes (Electrophoresis. 1998 Aug;19(11):1862-71):

10 “it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis” (page 1863, right column, full paragraph 2);

15 “The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts.” Page 1870 left column, last full paragraph;

Hancock (J Proteome Res. 2004 Jul-Aug;3(4):685):

20 “the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling” (full paragraph 2);

Allman (Blood. 1996 Jun 15;87(12):5257-68):

25 “germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations” (page 5257, paragraph bridging left and right columns);

Chen (Mol Cell Proteomics. 2002 Apr;1(4):304-13):

30 “The use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and

degradation, may influence the level of a protein present in a given cell or tissue.” (page 304, right column, full paragraph);

5 “Correlation analyses showed that protein abundance is likely a reflection of the transcription for a subset of proteins, but translation and post-translational modifications also appear to influence the expression levels of many individual proteins in lung adenocarcinomas.” Paragraph bridging pages 304 and 306;

10 Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 08/10/2005):

“other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made” (page 453, last full paragraph);

15 Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 2, 08/10/2005):

“the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps [from DNA to protein] is performed” (page 363, last full paragraph and page 364, Figure 6-90);

20 Lewin (Exhibit 3, 08/10/2005):

“production of RNA cannot inevitably be equated with production of protein” (paragraph bridging pages 847-848).

25 the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 3, 12/10/2004):

“... there have been published reports of genes for which such a correlation does not exist, ...” (paragraph 6);

25 Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9; Exhibit 5, 08/10/2005):

30 Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. Page 971, left column, first paragraph of introduction.

Even if one were to assume that the disclosed change in PRO874 transcripts could

35 reasonably be correlated with an assumed change in PRO874 polypeptide expression the skilled artisan still would not know if the assumed change in PRO874 polypeptide expression is tumor-dependent or tumor-independent because it is unknown if the disclosed change in PRO874

transcripts is tumor-dependent or tumor-independent. Neither the specification nor any of Applicants’ arguments, exhibits, declarations or other evidence provide any specific data

disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. A commonly understood general rule or dogma amounts to a showing that it is "not implausible" that invention will work for its intended purpose, which, in the face of the countervailing evidence, is insubstantial evidence of utility for the PRO874 polypeptide. The inherent lack of certainty in this general correlation results in a failure to prove practical utility for the PRO874 polypeptide and antibodies.

Because Applicants have failed to validate the significance of PRO874 gene expression to tumors and have failed to establish the correlation between PRO874 mRNA expression and PRO874 polypeptide expression in tumors, Applicants have failed to establish a significant probability that the PRO874 polypeptide and antibodies are useful as a cancer diagnostic or therapeutic. The specification lacks a sufficient correlation between the test performed on PRO874 mRNA expression and the asserted utility of the PRO874 polynucleotide and polypeptide. There is no reason for the skilled artisan to believe that it is more likely than not that the PRO874 polypeptide and antibodies could be used as a cancer diagnostic or therapeutic. The asserted utility of the PRO874 polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Regarding the requirement for further experimentation as a basis for lack of utility, utilities that

require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities (M.P.E.P. § 2107.01 I). In the present case, the asserted diagnostic or therapeutic utilities of the PRO874 gene, polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use because the skilled artisan would not know if or how PRO874 polypeptide expression would change in tumors.

Unlike the situation wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, in the present situation Applicants' have not provided any testing of the expression of the PRO874 polypeptide. In the absence of any information on the role, activity, or expression of the PRO874 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported change in PRO874 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO874 polypeptide expression would change in cancer. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the

statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in *Brenner v. Manson*:

5 But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO874 transcripts is tumor-dependent or tumor-10 independent and would not know if or how expression of the PRO874 polypeptide would change in tumors. The examiner concludes that Applicants' have failed to disclose how to use the claimed invention.

Applicants argue that they have established that the gene encoding the PRO874 polypeptide is differentially expressed in certain cancers compared to normal tissue and is useful 15 as a diagnostic tool, and therefore the corresponding polypeptide and antibodies are useful as diagnostic tools, as evidenced by the Grimaldi declaration (Exhibit 1, 12/10/2004). The declaration under 37 CFR 1.132 filed (Exhibit 1, 12/10/2004) is insufficient to overcome the rejection of claims 1-5 based upon the utility requirement of 35 U.S.C. § 101 as set forth in the last Office action because: The assertions that "Data from pooled samples is more likely to be 20 accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "The precise levels of gene expression are irrelevant" (paragraph 7), and "If a difference is detected, ... the gene and its corresponding polypeptide ... are useful for diagnostic purposes" (paragraph 7) are conclusory and

unsupported. Furthermore, the declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue, normal tissue, or any other type of tissue sample.

Applicants argue that the Office has mischaracterized Applicants' assertion of utility and 5 enablement. Applicants' arguments have been fully considered but they are not persuasive. The Grimaldi declaration (Exhibit 2, 12/10/2004) asserts that:

"Comparison of gene expression levels in normal versus diseased tissue has important implications both diagnostically and therapeutically." Paragraph 6.

10 "... identification of both gene expression and protein expression enables more accurate tumor classification ..." Paragraph 7.

The Ashkenazi declaration (Exhibit 5, 12/10/2004) asserts that:

15 the "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment." Paragraph 6.

Applicants are arguing that whatever the expression level and whatever the correlation, the PRO874 polypeptide and antibodies are useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not 20 disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are 25 expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

Applicants argue that they have established that the accepted understanding in the art is that there is a reasonable correlation between the level of mRNA and the level of the encoded protein. Applicants argue that it is well established that a change in the level of mRNA generally leads to a change in the level of the corresponding protein. Applicants argue that a necessary correlation is not required to establish an asserted utility, because there only need be a reasonable correlation. Applicants argue that the declarations of Grimaldi (Exhibit 2, 12/10/2004) and Polakis (Exhibit 3, 12/10/2004), as supported by Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 08/10/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 2, 08/10/2005), as further supported by Lewin (Exhibit 3, 08/10/2005), and as additionally supported by Zhigang (Exhibit 4, 08/10/2005) and Meric (Exhibit 5, 08/10/2005), establish that there is a positive correlation between changes in mRNA levels and changes in the corresponding protein levels. Applicants' arguments have been fully considered but they are not persuasive. There must be a necessary correlation between PRO874 mRNA expression and PRO874 polypeptide expression in order for the PRO874 polypeptide and antibodies thereto to function as the asserted cancer diagnostic or therapeutic. Applicants assume that for the PRO874 gene the analysis of transcript levels indicate the levels of PRO874 protein expression (Example 18, page 140, paragraph 00530). Haynes, Hancock, Allman, Chen, Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 08/10/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004 and Exhibit 2, 08/10/2005), Lewin (Exhibit 3, 08/10/2005), the declaration of Dr. Polakis under 37 CFR 1.132 (Exhibit 3, 12/10/2004) and Meric are evidence that the skilled artisan would not know if or how PRO874 polypeptide levels would change in tumors, as discussed above. Furthermore, the present specification only presents data showing a relative

difference in PRO874 mRNA levels. There is no evidence that PRO874 mRNA was highly expressed. Applicants have not provided any comparison of the levels of PRO874 polypeptide expression. Furthermore, the significance or relevance of the change in PRO874 transcripts cannot be ascertained because the skilled artisan would not know if the change is disease-

5 dependent or disease-independent, as supported by Hu and LaBaer. Even if one were to assume that the change in PRO874 transcripts could reasonably be correlated with a change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because one would not know if the change in PRO874 transcripts is disease-dependent or disease-independent.

10 The Grimaldi declaration (Exhibit 2, 12/10/2004) has been considered. However, in the present case it is unknown if the reported differences in PRO874 mRNA expression are tumor-dependent or tumor-independent. It is acknowledged that there are examples in the art where mRNA expression and protein expression correlate. However, there are examples where they do not correlate, as evidenced by Allman, Chen and the declaration of Dr. Polakis, as discussed
15 above. Applicants have not provided any testing of the role, activity, or expression of the PRO874 polypeptide. Furthermore, the declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue, normal tissue, or any other type of tissue sample.

Applicants refer to a declaration of Dr. Polakis filed with the response on 08/10/2005.

20 The declaration under 37 CFR 1.132 filed 12/10/2004 is insufficient to overcome the rejection of claims 1-5 based upon a lack of utility as set forth in the last Office action because: The facts to be established are whether or not the disclosed change in PRO874 transcripts is disease-

dependent or disease-independent and whether or not there is a correlation between the reported change in PRO874 transcripts and a change in PRO874 polypeptides levels in lung tumors as compared to their normal tissue counterparts. The declaration does not provide any data concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation 5 between the two in tumor tissue, normal tissue, or any other type of tissue sample. There is no evidence of record that either the PRO874 polynucleotide or the PRO874 polypeptide were abundantly expressed. The present specification does not teach the level of reproducibility or reliability of the results seen in Example 18. Given the paucity of information regarding PRO874 expression in tumors and the evidence in the art that there are numerous levels of 10 control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO874 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO874 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO874 polypeptide. Even if the examiner were to assume that the 15 disclosed change in PRO874 transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO874 transcripts is disease-dependent or disease-independent. While Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. 20 No data or results were presented for independent analysis. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer because 20% of the

cases examined do not show a correlation, according to Dr. Polakis. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because

5 there are examples of genes for which such a correlation does not exist, according to Dr. Polakis.

Molecular Biology of the Cell (Exhibit 1, 08/10/2005 and Exhibit 4, 12/10/2004 and Exhibit 2, 08/10/2005), Lewin (Exhibit 3, 08/10/2005), Zhigang (Exhibit 4, 08/10/2005), and Meric (Exhibit 5, 08/10/2005) are acknowledged. However, Molecular Biology of the Cell (Exhibit 1, 08/10/2005) acknowledges that “other controls can act later in the pathway from

10 DNA to protein to modulate the amount of gene product that is made” (page 453, last full paragraph). Molecular Biology of the Cell (Exhibit 4, 12/10/2004 and Exhibit 2, 08/10/2005) acknowledges that the final level of protein depends upon the efficiency with which each of the many steps from DNA to protein is performed (page 363, last full paragraph and page 364, Figure 6-90). Lewin (Exhibit 3, 08/10/2005) acknowledges that “production of RNA cannot

15 inevitably be equated with production of protein” (paragraph bridging pages 847-848).

Molecular Biology of the Cell and Lewin support and are consistent with the examiner’s position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the

20 technological field of the invention. The examiner does not agree that Figure 6-3, page 302 (Exhibit 4, 12/10/2004 and Exhibit 2, 08/10/2005) illustrates a basic principle that there is a correlation between increased gene expression and increased protein expression. This figure

only illustrates that different genes can be expressed with different efficiencies. Applicants have failed to explain the nexus between what this figure actually illustrates and what Applicants purport this figure to illustrate.

It is acknowledged that Zhigang (Exhibit 4, 08/10/2005) presents data showing a high 5 degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7; page 4 of 7, left column, full paragraph 1). Statistical certainty is not the issue. Zhigang supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. The present application fails to 10 disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Further experimentation would be required in order to identify or reasonably confirm a "real world" context of use.

It is acknowledged that Meric (Exhibit 5, 08/10/2005) states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression 15 between cancer cells and normal cells" (page 971, right column, first paragraph of "Introduction"). However, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO874 polypeptide. Therefore, the difference in PRO874 polypeptide expression between cancer cells and normal cells is unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in 20 cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of "Introduction"), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner's

position that the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

5 The examiner is not arguing that the techniques that measure gene levels, such as microarray analysis, differential display, and quantitative PCR, are without merit. The examiner is arguing that Applicants have failed to establish the correlation between PRO874 mRNA expression and PRO874 polypeptide expression in normal tissue, tumor tissue or any other type of tissue sample. Therefore, the probability that the asserted utilities are true is not ascertainable.

10 The skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. There is no reason for the skilled artisan to believe that it is more likely than not that the PRO874 polypeptide and antibodies thereto could be used as a cancer diagnostic or therapeutic.

Exhibits 6-9 are acknowledged. As Applicants recognize, each case must be decided on its own merits based on the evidence of record.

15 Applicants argue that Allman supports Applicants' position. Applicant's arguments have been fully considered but they are not persuasive. Unlike Allman (Blood. 1996 Jun 15;87(12):5257-68), Applicants have not provided any testing of the role, activity, or expression of the PRO874 polypeptide. The fact that it was unexpected that increases in BCL-6 protein were not correlated with a corresponding change in the level of BCL-6 mRNA only establishes

20 that the skilled artisan would not know if or how PRO874 polypeptide expression changes in tumors. The argument that Allman supports applicants' position because Allman did not obtain

the anticipated results is, in the face of the countervailing evidence, insubstantial evidence of utility for the PRO874 polypeptide.

The examiner does not agree that the caveat in Example 12 of the utility guidelines is applicable to the present situation because unlike the situation wherein the specification discloses 5 that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells, in the present case Applicants rely on a qualitative comparison of PRO874 mRNA expression between tumor tissue and normal samples in order to establish utility. However, the present specification does not teach the level of reproducibility or the level of reliability of the results seen in Example 18. The skilled artisan would not know if this 10 difference is disease-dependent or disease-independent. Furthermore, Applicants have not provided any testing of the expression, role, or activity of the PRO874 polypeptide. The skilled artisan would not know if or how expression of the PRO874 polypeptide would change in tumors. Even if the examiner were to assume that the reported change in PRO874 mRNA transcripts could reasonably be correlated with an assumed change in PRO874 polypeptide 15 expression, it still could not be ascertained if the assumed change in PRO874 polypeptide expression would be disease-dependent or disease-independent because the skilled artisan would not know if the change in PRO874 transcripts is disease-dependent or disease-independent.

Applicants' conclusion regarding the utility of the claimed invention has been considered but it is not persuasive. In the present case, the differential analysis of PRO874 transcripts does 20 not prove that the PRO874 polypeptide will perform as a cancer diagnostic or therapeutic. The differential expression of the PRO874 polynucleotide has not been adequately correlated with the contemplated cancer diagnostics or therapeutics of the PRO874 polypeptide or antibodies. The

PRO874 polynucleotide and polypeptide have not been tested to the extent that utility would be known to those of skill in the art.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the 5 claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that they have established a substantial, specific, and credible utility for the claimed antibodies that bind the PRO874 polypeptide. Applicant's arguments have been 10 fully considered but they are not persuasive. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails 15 as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and 20 conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claim Rejections - 35 USC § 112

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support for the limitation “amino acids 34-321 of SEQ ID NO: 10” cannot be found in the disclosure as originally filed, which raises the issue of new matter. Applicants argue that support for this limitation can be found in paragraph 0196. Applicant's arguments have been fully considered but they are not persuasive. Paragraph 0196 discloses that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides. However, the species methionine residue #34 as the starting amino acid is not supported by this generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. In other words, there is no evidence of record that the disclosure would not reasonably lead the skilled artisan to this particular species.

Applicants argue that the examiner misstates the test for compliance with the written description requirement. Applicants' arguments have been fully considered but they are not persuasive. The disclosure that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides makes it clear that Applicants have not adequately described “amino acids 34-321 of SEQ ID NO: 10” because

there is no evidence of record that amino acid #34 is employed as a start site. In the absence of any evidence that amino acid #34 is employed as a start site, the generic disclosure of what may be possible or conceivable does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention as now claimed.

5

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 10 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE 15 MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, 20 will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 1647

5 ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

10 IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

15 ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

20

DSR
DECEMBER 30, 2005